REMARKS

The specification has been amended to correct a typographical (spelling) error. Claims 1, 4 and 5 have been amended. Claims 9-18, 20-22 and 24 have been canceled. Claims 8, 19 and 23 have been withdrawn from consideration as being directed to a non-elected invention. Thus, claims 1, 3-8, 19 and 23 are now pending in the present application, with claims 1 and 3-7 currently under consideration. No new matter has been added. Reconsideration and withdrawal of the present objection and rejections in view of the comments presented herein are respectfully requested.

Objection to specification

The Examiner objected to the specification based on a typographical error at page 8, paragraph [0045]. Applicants presume that the Examiner intended to refer to page 18, paragraph [0045], which is where the typographical error appears. The specification as amended correctly recites "Type 2" rather than "Tape 2."

Claim Interpretation and Rejection under 35 U.S.C. § 112, second paragraph

The Examiner objected to the phrase "subject of Chinese descent" as not being defined, and rejected claims 1 and 3-7 under 35 U.S.C. § 112, second paragraph as allegedly being indefinite based on recitation of this term, since the specification did not provide a standard as to which individuals would be a "subject of Chinese descent." Claim 1 as amended recites a "subject of Chinese ancestry." The term "Chinese descent" is equivalent to "Chinese ancestry" as indicated by the following various definitions of the term "descent":

descent *n*

...

4. (Social Science / Anthropology & Ethnology) derivation from an ancestor or ancestral group; lineage

...

Collins English Dictionary – Complete and Unabridged 6th Edition 2003. © William Collins Sons & Co. Ltd 1979, 1986 © HarperCollins Publishers 1991, 1994, 1998, 2000, 2003

2. **descent** - properties attributable to your ancestry; "he comes from good origins"
extraction, origin
ancestry, filiation, lineage, derivation - inherited properties shared with others of your bloodline
full blood - descent from parents both of one pure breed

Based on WordNet 3.0, Farlex clipart collection. © 2003-2008 Princeton University, Farlex Inc.

descent
noun
...

4. origin, extraction, ancestry, lineage, family tree, parentage, heredity, genealogy, derivation *All the contributors were of foreign descent.*

Collins Thesaurus of the English Language – Complete and Unabridged 2nd Edition. 2002 © HarperCollins Publishers 1995, 2002

A person having ordinary skill in the art can readily determine whether a subject has Chinese ancestry. Accordingly, this term is clearly definite. As such, Applicants respectfully request reconsideration and withdrawal of the rejection under 35 U.S.C. § 112, second paragraph.

Rejections under 35 U.S.C. § 103(a)

Claims 1, 3-4, 6 and 7 were rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Liu et al. (*Diabet. Med.* **19**:113-118, 2002); Marre et al. *J. Clin. Invest.* **99**(7):1585-1595, 1997) and Neamat-Allah et al. *Diabet. Med.* **18**:906-914, 2001). In addition, Claim 5 was rejected under 35 U.S.C. § 103(a)) as allegedly being unpatentable over the combination of references listed above, and further in view of Norberg et al. (US 6,197,505); Ko et al. (*Diabetes* 44(7):727-732, 1995); and Buck et al. *BioTechniques* 27:528-536, 1999). However, as discussed below, these combinations of references do not render the present claims obvious.

In the Office Action As at page 8, the Examiner acknowledges that while Liu et al. teach polymorphic sequences comprising a (z-2) genotype of an ALR2 gene 5'-(CA) repeats, this reference does not teach an I/D genotype of an ACE gene; or a C106T genotype of an ALR2 gene in the promoter region. The Examiner cites Marre et al. which teaches the I/D genotype of an ACE gene which comprises a DD genotype; and Neamat-Allah et al. which teaches the C106T genotype of an ALR2 gene in the promoter region. In view of these teachings, the Examiner alleges that:

> *Since each genotype contributes towards development of diabetic nephropathy in diabetic subjects therefore, one of ordinary skill in the art has a reasonable expectation to expect that detection of a combination of two or more of these polymorphisms in a human will make that diabetic human being even more susceptible to developing diabetic nephropathy than other diabetics who lack these specific polymorphisms.*" (Emphasis added). (Office Action at page 10, first paragraph).

However, it is well known that human genetic makeup and human biology are complex. Thus, it cannot be assumed that positive effects observed with multiple polymorphisms will result in a greater susceptibility to development of diabetic nephropathy than will detection of a

single polymorphism. Positive effects observed in isolation may not necessarily result in additive (or synergistic) effects due to the complicated biological mechanisms and interactions involved. Indeed, it is possible that despite independently positive effects with several single polymorphisms, the simultaneous presence of two or more of these polymorphisms could neutralized the effect of a third polymorphism, or could result in the opposite effect.

For example, beta blockers and ACE inhibitors both lower blood pressure. However, their synergistic or additive effects are not well understood, likely due to complicated human biological mechanisms. Enclosed herewith as Exhibit A is a reference (Cleophas, TJM, Mechanisms offsetting the beneficial effects of antihypertensive drugs: a problem increasingly considered but incompletely understood. *Am. J. Ther.* **5**:413-419 (1998). Furthermore, an observed biological effects results from the interplay of a large number of variables, many of which are unknown and/or cannot be measured, all of which result in an observed phenotype.

Thus, contrary to the statements of the Examiner, one having ordinary skill in the art would not have any basis upon which to obtain a reasonable expectation of success in evaluating the presence of diabetic nephropathy by evaluating the presence of a particular set of polymorphic genes in a subject of Chinese ancestry, as presently claimed. In fact, the present inventors have discovered an unexpectedly more sensitive and accurate analysis than the prior art individual polymorphism analysis for the risk of diabetic nephropathy in subjects of Chinese ancestry.

The analysis in Example 2 of the present specification employed 711 Type 2 diabetic patients of Chinese ancestry and used complex modeling and machine learning to determine that the three polymorphisms recited in present claim 1 can combine to increase risk of nephropathy which varies among different individuals. As illustrated in Table 3 at page 18, the analysis with 3 risk genotypes increased the detection rate from 24.8% (176) to 40.8% (290). Many different genotypes could have been responsible or associated with risk of nephropathy. It is only based on Applicants' research that the three specific genotypes were identified, the combination of which was strongly correlated with risk of nephropathy. Thus, in the absence of Applicants' discovery, it would be difficult for one of ordinary skill in the art to predict that the detection of this combination of genotypes would successfully predict the risk of development of diabetic nephropathy without undue experimentation.

success is present in connection with the presently claimed invention. Moreover, in *KSR*, the court noted that "[w]hen there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense. In that instance the fact that a combination was obvious to try might show that is was obvious under § 103." (Emphasis added).

In the present case, there is no finite number of identified, predictable solutions to solve the technical problem of the present invention, as detection of many possible genotypes could have led to the solution. Moreover, in view of the complications and unpredictability of gene interactions discussed above, there is no basis for one of ordinary skill to conclude that the combination would reasonably lead to the anticipated success. Thus, the claims cannot be obvious in view of the cited references in any combination.

In view of the comments presented above, Applicants respectfully request reconsideration and withdrawal of the rejections under 35 U.S.C. § 103(a).

No Disclaimers or Disavowals

Although the present communication may include alterations to the application or claims, or characterizations of claim scope or referenced art, Applicant is not conceding in this application that previously pending claims are not patentable over the cited references. Rather, any alterations or characterizations are being made to facilitate expeditious prosecution of this application. Applicant reserves the right to pursue at a later date any previously pending or other broader or narrower claims that capture any subject matter supported by the present disclosure, including subject matter found to be specifically disclaimed herein or by any prior prosecution. Accordingly, reviewers of this or any parent, child or related prosecution history shall not reasonably infer that Applicant has made any disclaimers or disavowals of any subject matter supported by the present application.

CONCLUSION

Applicants submit that all claims are in condition for allowance. However, if minor matters remain, the Examiner is invited to contact the undersigned at the telephone number provided below.

Respectfully submitted,

KNOBBE, MARTENS, OLSON & BEAR, LLP

Dated: 11/23/09

By: _____

Neil S. Bartfeld, Ph.D.
Registration No. 39,901
Agent of Record
Customer No. 20,995
(619) 235-8550

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